

APPLICANTS: Moutsatos I. et al.  
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In the interview, the Examiner stated that he would withdraw the 35 U.S.C. §103 rejection as set forth on the February 7, 2002 Office Action, and allow claims 11, 12, 14-17 and 19-23 directed to the ex-vivo engineered cells of bone morphogenic protein 2 (BMP-2) gene transformed progenitor cells, prior to implantation for stimulating bone growth/repair, based on a Declaration demonstrating that: (1) *a priori* one skilled in the art would not have had a credible expectation that ex-vivo engineered cells of BMP-2 transformed cells for implantation in order to stimulate bone growth/repair was obtainable; and (2) that the implantation of the ex-vivo engineered cells provided unexpected results.

**REJECTION UNDER 35 U.S.C. § 103:**

In the Office Action, the Examiner asserted that claims 11, 12, 14-17 and 19-23 are rejected under 35 U.S.C. § 103 as allegedly being unpatentable over US Patent No. 5,763,416, or WO 96/39431 in view of US Patent No. 5,645,084, and US Patent No. 5,700,774. The Examiner asserted that based on US Patent No. 5,763,416, or WO 96/39431 in view of US Patent No. 5,645,084 and US Patent No. 5,700,774, it would have allegedly been obvious to one of ordinary skill in the art to combine the patent's description of the invention with the references listed, to make the claimed invention, that of ex-vivo culture of bone marrow progenitor cells transformed with BMP-2 prior to implantation for stimulating bone growth/repair.

In response, Applicants traverse the rejection of claims 11, 12, 14-17 and 19-23 under 35 U.S.C. § 103. Applicants maintain that US Patent No. 5,763,416 or WO 96/39431, further in view of US Patent No. 5,645,084 and US Patent No. 5,700,774, do not render the instant invention obvious, nor would a person of ordinary skill in the art have had a reasonable and/or credible expectation of success in producing the instant claimed invention given the teachings of US Patent No. 5,763,416 or WO 96/39431, with US Patent No. 5,645,084 and US Patent No. 5,700,774.

Claim 11 is directed to a method for producing cells for implantation at the site of a bone infirmity in a human, said method comprising the steps of:

- (a) transforming a cultured human progenitor cell or a bone marrow stromal cell with a DNA encoding bone morphogenesis protein 2 (BMP-2); and
- (b) culturing the cultured human progenitor cell or bone marrow stromal cell transformed in step (a), whereby cells are produced for implantation at the site of a bone infirmity in a human.

Applicants maintain that direct *in-vivo* gene transfer is not *a priori* predictive for use of *ex-vivo* engineered cells for implantation for bone repair regeneration, and thus there is no reasonable basis for one to obtain the claimed invention based on the references cited by the Examiner. Further, there is no credible basis to support the assertion of the Examiner that it would be obvious for one skilled in the art to obtain the subject matter defined by the claims based on the cited references. Bone repair as claimed results from the action of both the autocrine and paracrine mechanisms due to implantation of *ex-vivo* engineered BMP-transformed cells. While direct *in-vivo* gene transfer does not provide autocrine and paracrine mechanistic actions.

Without credible support, such as experimental evidence, the cited references fail to render obvious the subject matter defined by the claims. The cited references do not provide any support or evidence for the use of *ex-vivo* engineered cells for implantation to repair bone. Thus, the cited references cannot render obvious the subject matter defined by the claims.

In addition, it was unexpected that *ex-vivo* engineered cells implanted for bone regeneration would achieve a higher efficiency of bone repair regeneration in comparison to the described *in-vivo* therapy of Bonadio.

In support of the foregoing, Applicants attach hereto as Appendix 1, a Declaration by Dr. Dan Gazit.

Thus, as demonstrated in the Declaration, i) *a priori* one skilled in the art would not have had a reasonable expectation of success based on *in-vivo* methods, such as Bonadio, that bone repair regeneration would result from *ex-vivo* engineered cells implanted; ii) there is no credible basis to support the assertion of the Examiner that it would be obvious for one skilled in the art to obtain the subject matter defined by the claims based on the cited references; and

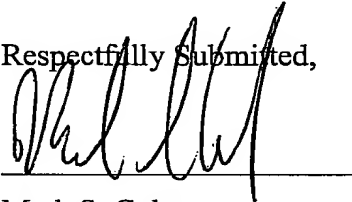
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iii) it was unexpected that as a result of such *ex-vivo* engineered cells implanted a higher efficiency of functional bone regeneration would be achieved. Therefore, contrary to the Examiner's assertion, the cited references do not render Applicants' invention obvious. Accordingly, Applicant requests the Examiner to reconsider and withdraw the rejection of the claims under 35 U.S.C. 103.

Based on the foregoing, the pending claims are deemed to be allowable. Their favorable reconsideration and allowance is respectfully requested. Should the Examiner have any question or comment as to the form, content or entry of this Communication, the Examiner is requested to contact the undersigned at the telephone number below.

The undersigned Attorney hereby authorizes the United States Patent and Trademark Office to charge Deposit Account No. 05-0649 for any fees required.

Respectfully Submitted,



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